Annals of Oncology 26: 529–535, 2015
doi:10.1093/annonc/mdu561
Published online 5 December 2014

Patterns of practice of regional nodal irradiation in breast cancer: results of the European Organization for Research and Treatment of Cancer (EORTC) NOdal Radiotherapy (NORA) survey†

Y. Belkacemi[1,2*], O. Kaidar-Person[2,3], P. Poortmans[4], M. Ozsahin[2,5], M-C. Valli[6], N. Russell[7], I. Kunkler[8], J. Hermans[9], A. Kuten[2,3,10], G. van Tienhoven[11] & H. Westenberg[12], on behalf of the Breast Working Party of the EORTC Radiation Oncology Group (ROG)

[1]APHP, GH Henri Mondor Breast Center, Radiation Oncology Department, University Paris-East Creteil, France; [2]Association of Radiotherapy and Oncology of the Mediterranean Area (www.aromecancer.org); [3]Department of Radiation Oncology, Rambam, Haifa, Israel; [4]Department of Radiation Oncology, Radboud University Medical Centre, Nijmegen, The Netherlands; [5]Department of Radiation Oncology, CHUV, Lausanne; [6]Radiation Oncology Department, Oncology Institute of Southern Switzerland, Switzerland; [7]Department of Radiotherapy, The Netherlands Cancer Institute, Amsterdam, The Netherlands; [8]Edinburgh Cancer Centre, University of Edinburgh, Edinburgh, UK; [9]EORTC Breast Working Party of the Radiation Oncology Group (ROG), EORTC, Brussels, Belgium; [10]Italian Hospital, Haifa, Israel; [11]Department of Radiation Oncology, Academisch Medisch Centrum, Amsterdam; [12]Institute for Radiation Oncology Arnhem (ARTI), Arnhem, The Netherlands

Received 14 September 2014; revised 29 October 2014 and 23 November 2014; accepted 24 November 2014

Background: Predicting outcome of breast cancer (BC) patients based on sentinel lymph node (SLN) status without axillary lymph node dissection (ALND) is an area of uncertainty. It influences the decision-making for regional nodal irradiation (RNI). The aim of the NORA (NOdal RAdiotherapy) survey was to examine the patterns of RNI.

Methods: A web-questionnaire, including several clinical scenarios, was distributed to 88 EORTC-affiliated centers. Responses were received between July 2013 and January 2014.

Results: A total of 84 responses were analyzed. While three-dimensional (3D) radiotherapy (RT) planning is carried out in 81 (96%) centers, nodal areas are delineated in only 51 (61%) centers. Only 14 (17%) centers routinely link internal mammary chain (IMC) and supraclavicular node (SCN) RT indications. In patients undergoing total mastectomy (TM) with ALND, SCN-RT is recommend by 5 (6%), 53 (63%) and 51 (61%) centers for patients with pN0(i+), pN(mi) and pN1, respectively. Extra-capsular extension (ECE) is the main factor influencing decision-making RNI after breast conserving surgery (BCS) and TM. After primary systemic therapy (PST), 49 (58%) centers take into account nodal fibrotic changes in ypN0 patients for RNI indications. In ypN0 patients with inner/central tumors, 23 (27%) centers indicate SCN-RT and IMC-RT. In ypN1 patients, SCN-RT is delivered by less than half of the centers in patients with ypN(i+) and ypN(mi). Twenty-one (25%) of the centers recommend ALN-RT in patients with ypN(mi) or 1–2N+ after ALND. Seventy-five (90%) centers state that age is not considered a limiting factor for RNI.

Conclusion: The NORA survey is unique in evaluating the impact of SLNB/ALND status on adjuvant RNI decision-making and volumes after BCS/TM with or without PST. ALN-RT is often indicated in pN1 patients, particularly in the case of ECE. Besides the ongoing NSABP-B51/RTOG and ALLIANCE trials, NORA could help to design future specific RNI trials in the SLNB era without ALND in patients receiving or not PST.

Key words: radiotherapy, breast cancer, sentinel lymph node, axillary dissection, internal mammary chain, supraclavicular node

*Correspondence to: Prof. Y. Belkacemi, Université de Paris XII, CHU Henri Mondor, 51 Av Mal De Lattre de Tassigny, Créteil 94000, France. Tel: +33-1-49-81-45-22; Fax: +33-1-49-81-25-89; E-mail: yazid.belkacemi@hmn.aphp.fr

†Presented at the 56th Annual Meeting of the American Society for Therapeutic Radiology and Oncology (San Francisco, September 2014) and at the 37th Annual SABCS (San Antonio, December 2014), USA.

introduction

Predicting breast cancer (BC) outcome based on sentinel lymph node (SLN) status without axillary lymph node dissection (ALND) is a new area of uncertainty for regional nodal irradiation (RNI) in the adjuvant setting or after primary systemic therapy (PST).

The updated clinical practice guidelines report from the American Society of Clinical Oncology [1] concluded that for patients with early-stage BC with negative SLN and those with 1–2 metastatic SLN receiving whole breast irradiation (WBI) should not undergo ALND. Conversely, women with SLN metastases who will undergo total mastectomy (TM) should be offered ALND. These recommendations are mainly based on two randomized trials [2, 3]. However, several concerns remain about these trials including the short follow-up and the uncertain coverage of the axilla by the tangential fields (TgF) used with three-dimensional conformal radiotherapy (3D-CRT) [4]. In addition, (i) the risk of non-SLN involvement in the axilla depends on the size of SLN metastasis, (ii) locoregional disease control is important for survival and quality of life, (iii) RNI increases disease-free and overall survival [5–7] and (iv) axillary lymph node radiotherapy (ALN-RT) can allow equivalent regional control to ALND in SLN-positive patients [8].

Having appreciated the importance of RNI in the era of modern radiotherapy and axillary surgery, some national groups have published guidelines with particular attention to RNI [9, 10]. However, these guidelines are not widely implemented nationally and decision-making still depends mainly on local policy.

The NORA (NOdal RAdiotherapy) survey was designed to examine the patterns of RNI practice in European Organization for Research and Treatment of Cancer (EORTC) affiliated centers according to different clinical scenarios observed after SLNB followed or not by ALND in patients undergoing breast-conserving surgery (BCS) or TM with or without PST. The results may help to provide a basis for designing future trials in areas of equipoise in clinical decision-making concerning RNI.

methods

NORA survey was designed to examine the contemporary practice of RNI in EORTC centers. The web-questionnaire was distributed to 88 EORTC centers. Responses from representative of the affiliated centers were registered between July 2013 and January 2014.

The questionnaire included four sections. The first section was dedicated to the BC-related workload, local radiotherapy indications and planning protocols. The rest of the questionnaire has focused on RNI indications after BCS or TM with or without PST. In each of the scenarios, questions were addressed regarding SLNB either followed or not by ALND, and included all nodal involvement status, from tumor cells to ≥10N+. For each situation, internal mammary chain (IMC-RT), supra/infraclavicular (SCN-RT) and ALN-RT indications were questioned.

results

institutions and local policy for radiotherapy practice

The distribution of centers, the number of patients treated per month, the use of multidisciplinary meetings and radiotherapy technique validation are presented in Table 1.

Table 1. Practice in the centers and radiotherapy technique

	n	%
Centers		
Comprehensive cancer centers	45	54
University hospitals	18	21
Public community hospitals	16	19
Private facilities	5	6
No. of BC patients per month		
>25	34	40
25–50	29	35
>50	21	25
Validation of RT multidisciplinary meeting		
Yes	80	95
No	4	5
Validation of RT in a technical board meeting		
Yes	69	82
No	15	18
3D-CRT planning to all patients		
Yes	81	96
No	3	4
Nodal systematic delineation		
Yes	51	61
No	33	39

3D-CRT, three-dimensional conformal radiotherapy; BC, breast cancer.

RNI after BCS

When IMC-RT is indicated (for N-, central/inner tumors, for example), only 14 (17%) centers reported to systematically indicate additional SCN-RT. Only half of the centers advocated SCN-RT for intermediate risk patients (1–3N+). For macrometastatic SLN involvement in patients without ALND, 13 (5%), 55 (65%) and 48 (57%) centers recommended RNI involving IMC, SCN and ALN, respectively (Table 2).

Regarding the radiotherapy technique used for axillary coverage, 21 (25%) centers responded that TgF are sufficient to cover residual axillary disease in patients with positive SLNs without ALND.

RNI post-mastectomy

In post-mastectomy radiotherapy (PMRT), adverse standard pathological prognostic factors did not impact volume definition for RNI. SCN-RT was recommended as a standard of care for patients with pN0(i+), pN(mi) and pN1 disease in 5 (6%), 53 (63%) and 51 (61%), respectively. Extra-capsular extension (ECE) is considered as the main factor for ALN-RT indication. Furthermore, 34 (40%) centers prescribe ALN-RT in patients with ≥3–4 positive LNs after ALND, irrespective of the number of examined axillary LNs (Table 2).

RNI after PST

Out of 84 centers, 68 (81%) use pre-PST imaging±biopsy for staging and 63 (75%) declared that the pre-PST nodal status dictates volumes definition for RNI.

Table 2. Nodal radiotherapy after breast conservative surgery or total mastectomy

Radiotherapy after breast conservative surgery			
Systematic SCN-RT if IMC is indicated	*n*	%	
Yes	14	17	
No	70	83	
Nodal RT volumes according to SLN status (with ALND)			
Nodal status	IMC-RT (*n*)	SCN-RT (*n*)	ALN-RT (*n*)
pNi+	0	3 (4%)	3 (4%)
pNmicro	2 (2%)	20 (24%)	6 (7%)
pNmacro	11 (13%)	55 (65%)	2 (2%)
Nodal RT volumes according to SLN status (without ALND)			
pNi+	1 (1.2%)	7 (8%)	12 (14%)
pNmicro	4 (5%)	29 (34%)	29 (34%)
pNmacro	13 (15%)	55 (65%)	48 (57%)
Tangential fields involve axilla for potential residual disease			
	n	%	
Yes	21	25	
No	63	75	
Radiotherapy after total mastectomy			
	pNi+	pNmi	pN1
SCN-RT indications	5 (6%)	53 (63%)	51 (60%)
SCN-RT	—	9 (11%)	—
ECE (−)	—	—	16 (19%)
ECE (+)	—	—	25 (30%)
ALN-RT	—	—	
3–4N+	—	—	34 (40%)

SLN, sentinel lymph node (biopsy); ALND, axillary lymph node dissection; RT, radiotherapy; SCN-RT, supraclavicular radiotherapy; IMC-RT, internal mammary chain radiotherapy; ALN-RT, axillary lymph node radiotherapy; pN: pathologic nodal status.

In patients with ypN0, 67 (80%) centers do not routinely prescribe RNI. Nodal volume definition take into account the final pathological fibrotic changes observed in the axillary LNs in 49 (58%) centers. In ypN0 patients with inner and centrally located tumors, 32 (39%) centers treat the SCN area either alone or including IMC in 23 (27%) centers (Table 3).

Nodal irradiation in elderly patients

Out of 84 centers, 82 (98%) reported that RNI is not particularly omitted in patients >70 years of age. Seventy-five centers (90%) responded that they had no fixed upper age limit for RNI.

discussion

The term, RNI, is not uniformly defined in the literature. In historic series, RNI was used to describe large nodal irradiation. After surgery including ALND, ALN-RT and IMC-RT indications have declined over time, because of the low benefit/risk ratio for arm lymphedema and increased risk of vascular and cardiac morbidity/mortality. On the other hand, it is widely recognized that advances in radiotherapy techniques, and systematic multidisciplinary validation of indications have contributed to a marked decrease in late toxicity [11]. In the NORA survey, 80 (95%) centers stated that radiotherapy indications are confirmed at a multidisciplinary meeting and 69 (82%) routinely validate volumes and technique in a dedicated meeting. However, nodal areas are delineated in only 51 (61%) centers. LNs area delineation is particularly important for evaluation of nodal coverage when the complete axillary status is unknown [4]. Before the advent of 3D-CRT, the evaluation of the dose distribution of RNI was impossible. These considerations also apply for recent studies that provide new evidence of the survival benefit of RNI [5–7].

RNI by site

In contrast to PMRT [12], the benefit from separate irradiation of the different nodal areas has never been investigated in a randomized trial after BCS. Thus, it is difficult to quantify the contribution to improved outcome achieved by radiotherapy of the distinct sites. Table 4 summarizes an overview of RNI published data, guidelines and NORA survey results.

supraclavicular node radiotherapy

RNI indications and volumes are generally based on clinicopathological factors [10]. Yu et al. [13] reported a close relationship between 5-year SCN failure and reduced overall survival in 448 pN1 patients without radiotherapy. Also, ECE was one of the main independent risk factors. When considering only patients with 1–3N+, SCN recurrence has a deleterious impact on outcome with

Table 3. Nodal radiotherapy after primary systemic therapy and surgery

Decision for nodal RT according to pretreatment nodal status			
	n	%	
Yes	63	75	
No	21	25	
Decision for nodal RT according to post-operative fibrotic scars in pN0 patients			
Yes	49	58	
No	35	25	
Decision for nodal RT in pN0 patients with an unknown pre-PST nodal status			
Yes	59	70	
No	25	30	
Decision for nodal RT in proven pN0 pre-PST nodal status			
Yes	17	20	
No	67	80	
Decision for nodal RT in after PST			
Volumes	SCN-RT (*n*)	IMC-RT (*n*)	ALN-RT (*n*)
ypN0 BUT inner or central tumors	23 (27%)	32 (38%)	—
ypN0i+	22 (26%)	6 (7%)	—
ypNmi	30 (36%)	8 (10%)	—
ypN+ (1N+)	44 (52%)	12 (14%)	21 (25%)
ypN+ (2N+)	58 (69%)	15 (18%)	
ypN+ (≥ 3N+)	67 (80%)	26 (31%)	34 (40%)

ALND, axillary lymph node dissection; RT, radiotherapy; SCN-RT, supraclavicular radiotherapy; IMC-RT, internal mammary chain radiotherapy; ALN-RT, axillary lymph node radiotherapy; pN, pathologic nodal status.

only 18% of survival at 10 years [14]. In the NORA survey, 55 (65%) centers indicate at SCN-RT in the case of nodal macrometastatic disease irrespective of SLN or ALND. This rate was lower (34%) in the case of micrometastatic SLN involvement without ALND (Table 2). In Canada, the use of SCN-RT in patients with 1–3N+ increased from 23% prior 1997 to 57% thereafter [15]. This was probably due to: (i) the publication of the late results of the PMRT trial that showed a benefit of PMRT including comprehensive RNI for pN1 patients [16] and (ii) the improved 10-year locoregional control by RNI in a large retrospective analysis of 2768 pN1 from the British Columbia database [15].

In terms of recommendations, while the early German (S3 and AGO) [17] guidelines were more restrictive with regard to SCN-RT indications, others such as the French [10], the US-NCCN and the recent German Society of Radiation Oncology (DEGRO) guidelines do recommend systematic SCN-RT for patients with 1–3N+ [1, 8, 10]. However, these guidelines cannot distinguish the contribution of SCN-RT from the potential effect of IMC-RT on outcome. They are mainly based on the balance between high risk of SCN recurrence and the fear toxicity of IMC-RT. This benefit/risk ratio has advocated the wide use of SCN-RT without IMC-RT in North America [18]. The NORA survey showed that a very low rate of centers (17%) systematically link SCN-RT indication to IMC-RT.

internal mammary chain radiotherapy

It is important to distinguish BCS and PMRT studies for IMC-RT indications. IMC-RT was part of the treatment in most PMRT studies [16, 19] and the two major randomized trials investigating RNI [5, 6]. Only the French randomized trial has specifically addressed the question of IMC-RT contribution as part of PMRT [12]. This trial included 1334 patients who had chest wall and SCN-RT and were randomized to receive or not IMC-RT. The authors conceded that the study might have been underpowered to prove any significant survival benefit for IMC-RT. They admitted that their data do not permit a definite conclusion [12]. These results are in contrast to the large French cohort study on 1630 patients, which showed a significant survival benefit at 10 (+12%) and 20 years (+24%) of IMC-RT in patients with medial/central tumors [20].

In the European EORTC 22922-10925 study, the question of IMC-RT was addressed in 4004 patients among whom 23% had PMRT. They concluded that IMC-RT should be recommended for patients with involved axillary LNs and/or medially located tumors. Further, in the MA20 trial, RNI, defined as target volume including axilla levels I-III, SCN and IMC nodes, increased locoregional control and survival without distant metastases [6].

In terms of guidelines, the NCCN [1] states that IMC-RT should be 'strongly considered' for pN1 patients, regardless of the number of affected nodes and irrespective of type of surgery and even for pN0 patients with tumors ≥5 cm after TM. The French guideline recommends, 'SCN and IMC nodes should be systematically irradiated in patients with internal-central tumors and pN1' [10]. The NORA survey showed that centers consider IMC-RT indications differently from the other nodal areas in the case of macrometastatic SLN involvement without ALND. Only 13 (15%) centers recommend IMC-RT, while 55 (65%) and 48 (57%) centers indicated SCN-RT and ALN-RT, respectively. It should be noted that the survey was conducted before the results of the analysis of the EORTC 22922-10925 trial were known [5].

axillary lymph node radiotherapy

The other controversy concerns axillary irradiation indications in the SLNB era [21]. It has been shown in randomized trials that SCN-RT plus ALN-RT, which are systematically linked as one RT volume, is as effective and less toxic than ALND alone [8]. Thus, with the widespread introduction of the SLNB procedure for staging and the consequently decreased use of ALND, the latter procedure may be increasingly replaced by ALN-RT.

In the NORA survey, 48 (57%) and 55 (65%) of centers indicate, respectively, SCN-RT and ALN-RT in cases of macrometastatic SLN involvement without ALND. In patients with ≥3–4N+, 40% of the centers prescribe ALN-RT irrespective of the number of examined axillary LNs with a significant impact of ECE status on volume definition.

In the French consensus statement, only patients 'with massive involvement after ALND and those who have no ALND' should undergo axillary radiotherapy [10]. Recently, the DEGRO panel stated, 'data do not permit ultimate conclusions whether any local treatment of the axilla can be safely omitted in selected patients with 1–2 involved LNs or in case of micrometastases'. In cases of macroscopic SLN metastases, they concluded that

Table 4. Regional nodal irradiation by site published in the literature and guidelines

SCN-RT±IMC-RT indication				
Criteria	Retrospective literature	Randomized trials	National guidelines [1, 10, 11, 21]	NORA survey
pN0	No SCN-RT needed for pN0	MA20: benefit for only high-risk patients [7] EORTC: inner/central tumors [6]	Not recommended	Indications in inner/central tumors: 23% (SCN-RT) and 32% (IMC-RT) of centers
Macrometastasis	RNI did not affect the rate of axillary failure or supraclavicular failure in patients with 1–3 N+ [17]	Benefit for RNI [7]	Similar to 1−N+ but not particularly specified	SCN-RT in 55 (65%) centers IMC-RT in 11 (13%) centers
1–3 N+	Loco-regional±survival benefit [18, 20, 24] IMC-RT: survival benefit [24]	PMRT: OS benefit [20, 23] Data from EORTC and MA20 for RNI [6, 7] Increase indication of SCN-RT in Canada (57%) [19]	Restrictive in early German S3 guidelines [10] Systematic SCN-RT: French [11] DEGRO [10] NCCN [1]	Indication declared by 50% of the centers ECE: main factor for decision-making
≥4 N+	Loco-regional±survival benefit [18, 20, 24] IMC-RT: survival benefit [24]		RNI irradiation indicated	Indicated by 40% of the centers
		ALN-RT		Indications
	Guidelines			NORA survey
	NCCN [1]	French [11]	DEGRO [10, 21]	
Criteria	*BCS and SLNB:* 1 or 2 positive SLN: no ALD if WBI (tangential fields)	Positive SLN and no ALND Massive involvement of LNs in ALND	*SLNB without ALND* Indication for: 1–2 LNs + Micrometastasis Macrometastases	*SLNB without ALND:* pNmi: 29 (34%) centers pNmacro: 48 (57%) *SLNB and ALND:* pNi+ to pNmacro: <7%

ALND, axillary lymph node dissection; SLNB, sentinel lymph node biopsy; RT, radiotherapy; RNI, regional nodal irradiation; SCN-RT, supraclavicular radiotherapy; IMC-RT, internal mammary chain radiotherapy; ALN-RT, axillary lymph node radiotherapy; pN, pathologic nodal status.

ALN-RT (as part of RNI) should be discussed as an alternative to ALND [9]. The German recommendations are mainly based on the AMAROS trial results showing that ALN-RT and ALND provided both excellent and comparable locoregional control and survival at 5 years with, however, significantly increased incidence of arm lymphedema in the latter [8]. However, the design and the results of the AMAROS may raise discussion regarding: (i) the potential 'overtreatment' using extensive RNI including axilla levels, (ii) the imbalance in the distribution of SNL-positive patients in the two arms, (iii) the 5-year axillary recurrence rate which was far below that hypothesized and (iv) the short follow-up which could not result in enough axillary recurrences for sufficient statistical power and better evaluation of late cardiac toxicity.

When ALN-RT is indicated, the debate concerns the technique and dose optimization. The excellent outcome observed in the ACOSOG-Z0011 trial was attributed to the coincident dose to the axilla delivered by the TgF used to treat the breast volume [2]. Radiotherapy nodal volumes details were available from the report forms of only 605 patients. The radiotherapy charts could be reviewed in only 288 patients. No clear conclusion could be drawn from the analysis on whether additional RNI was necessary or beneficial for these patients [22].

A compromise accounting for a potentially increased risk of locoregional recurrence of SLN-positive patients was proposed by Henri Mondor team. Their approach to use 'high TgF' or 'direct fields' to cure potential axillary residual disease was supported by the limited coverage of axillary contents including the SLNB area when only standard TgF are planned to treat the axilla [4, 21]. In the NORA survey, only 21 (25%) centers declared that TgF cover residual axillary disease adequately in SLN-positive patients without ALND.

RNI by site after PST and surgery

PST is the accepted approach for women with locally advanced BC for whom immediate surgery is not feasible. Usually, an ultrasound-guided fine needle aspiration of suspicious nodes is carried out before PST to determine axillary nodal status. The NORA survey showed that 68 (81%) centers use pre-PST imaging and/or biopsy for staging.

The indications for adjuvant radiotherapy in patients who underwent PST are generally based on similar prognostic factors as those used to indicate radiotherapy following primary BCS or TM [10]. Therefore, the pre-PST disease criteria are important as they often dictate the RNI volumes. In NORA survey, 63

(75%) centers declared that the pre-PST nodal status dictated their decision for RNI. In ypN0 patients, 67 (80%) centers do not advocate RNI, while 49 (58%) centers reported taking into account the pathological fibrotic changes observed in the axillary LNs of ypN0 patients with an unknown nodal status before PST. The ongoing NSABP-B51/RTOG trial was designed to test RNI in patients with positive ALNs before PST who converted to ypN0 either after TM or BCS [23].

In cases of ypN1, there were predictably a higher number of centers that indicate RNI by site according to the degree of involvement. SCN-RT is delivered by 36–80% of the centers in patients with ypN(i+) to >3–4N+ disease. Axillary volume alone is irradiated in 25% and 40% of the centers in patients with ypN (mi) or 1–2N+ and >3–4N+ disease, respectively. These differences between centers probably reflect uncertainties among radiation oncologists on the indications for RNI and appropriate volumes in the adjuvant setting. The ongoing phase III ALLIANCE trial has been designed in patients with cT1-3N1 BC to compare ALND with axillary irradiation in patients with residual 1–6 SLN/non-SLN-positive after PST [23].

RNI in elderly patients

While Oxford overview of BCS trials showed a twofold reduction in first relapse even in 'low risk' older patients, the recent report from the SIOG-task force could not draw any RNI guidelines for BC elderly patients [24]. Indeed, RNI has never been considered as a relevant question for elderly patients. Conversely, when considering breast radiotherapy, the CALGB9343 trial showed in patients aged ≥70 year with tumors ≤2 cm, a superiority of combined WBI+tamoxifen over tamoxifen alone in terms of local control. However, this gain did not translate into an advantage for 10-year survival [25]. In NORA survey, adjuvant RNI indication is neither restricted by an upper age limit (90% of the centers) nor omitted in patients over 70 years (98% of the centers).

conclusion

NORA is the first survey that aimed to evaluate the practice of RNI by site in the contemporary context of SLNB and 3D-CRT. ALN-RT is indicated by 40% of the centers in patients with ≥3–4 positive LNs, irrespective of the number of nodes examined in the ALND. New trials testing RNI in the SLN micro/macrometastases patients are needed.

In the PST setting, the large majority of the centers do not indicate RNI in ypN0 patients. While ALLIANCE trial aims to determine the best nodal management option (ALND versus RNI) in post-PST SLN/non-SLN-positive patients, and NSABP-B51/RTOG investigate the need of RNI in complete responders, questions on RNI indications by sites and by BC molecular subtypes are pending. Additionally, a trial investigating RNI in ypN0 patients with pre-PST cN0 or Nx status could help to determine the role of radiotherapy in locoregional control and its impact on survival.

funding

This publication is supported by Fonds Cancer (FOCA) from Belgium (no grant number).

disclosure

The authors have declared no conflicts of interest.

references

1. Lyman GH, Temin S, Edge SB et al. Sentinel lymph node biopsy for patients with early-stage breast cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 2014; 32(13): 1365–1383.
2. Giuliano AE, McCall L, Beitsch P et al. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: the American College of Surgeons Oncology Group Z0011 randomized trial. Ann Surg 2010; 252(3): 426–432.
3. Krag DN, Anderson SJ, Julian TB et al. Sentinel lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomized phase 3 trial. Lancet Oncol 2010; 11: 927–933.
4. Belkacemi Y, Allab-Pan Q, Bigorie V et al. The standard tangential fields used for breast irradiation do not allow optimal coverage and dose distribution in axillary levels I–II and the sentinel node area. Ann Oncol 2013; 24(8): 2023–2028.
5. Poortmans P. Irradiation of the internal mammary and medial supraclavicular lymph nodes in stage I to III breast cancer: 10 years results of the EORTC Radiation Oncology and Breast Cancer Groups phase III trial 22922/10925. Eur J Cancer 2013; 47(Suppl 2).
6. Whelan T. NCIC-CTG MA20 an intergroup trial of regional nodal irradiation in early breast cancer. J Clin Oncol 2011; 29(Suppl): (abstr LBA1003).
7. Budach W, Kammers K, Boelke E, Matuschek C. Adjuvant radiotherapy of regional lymph nodes in breast cancer—a meta-analysis of randomized trials. Radiother Oncol 2013; 8: 267.
8. Donker M, van Tienhoven, Straver ME et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. Lancet Oncol 2014; 15: 1303–1310.
9. Sautter-Bihl ML, Sedlmayer F, Budach W et al. DEGRO practical guidelines: radiotherapy of breast cancer III—radiotherapy of the lymphatic pathways. Strahlenther Onkol 2014; 190(4): 342–351.
10. Belkacemi Y, Fourquet A, Cutuli B et al. Radiotherapy for invasive breast cancer: guidelines for clinical practice from the French expert review board of Nice/Saint-Paul de Vence. Crit Rev Oncol Hematol 2011; 79(2): 91–102.
11. Taylor C, Shewbridge A, Harris J, Green JS. Benefits of multidisciplinary teamwork in the management of breast cancer. Breast Cancer 2013; 5: 79–85.
12. Hennequin C, Bossard N, Servagi-Vernat S et al. Ten-year survival results of a randomized trial of irradiation of internal mammary nodes after mastectomy. Int J Radiat Oncol Biol Phys 2013; 86(5): 860–866.
13. Yu JI, Park W, Huh SJ et al. Determining which patients require irradiation of the supraclavicular nodal area after surgery for N1 breast cancer. Int J Radiat Oncol Biol Phys 2010; 78(4): 1135–1141.
14. Yates L, Kirby A, Crichton S et al. Risk factors for regional nodal relapse in breast cancer patients with one to three positive axillary nodes. Int J Radiat Oncol Biol Phys 2012; 82(5): 2093–2103.
15. Wai ES, Lesperance M, Speers CH et al. Increased use of regional radiotherapy is associated with improved outcome in a population-based cohort of women with breast cancer with 1–3 positive nodes. Radiother Oncol 2010; 97(2): 301–306.
16. Ragaz J, Olivotto IA, Spinelli JJ et al. Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. JNCI 2005; 97(2): 116–126.
17. Sautter-Bihl M-L, Souchon R, Budach W et al. DEGRO practical guidelines for radiotherapy of breast cancer II. Strahlenther Onkol 2008; 184: 347–353.
18. Ceilley E, Jagsi R, Goldberg S et al. Radiotherapy for invasive breast cancer in North America and Europe: results of a survey. Int J Radiat Oncol Biol Phys 2005; 61(2): 365–373.
19. Overgaard M, Nielsen HM, Overgaard J. Is the benefit of postmastectomy irradiation limited to patients with four or more positive nodes, as recommended in international consensus reports? A subgroup analysis of the DBCG 82 b&c randomized trials. Radiother Oncol 2007; 82(3): 247–253.

20. Courdi A, Chamorey E, Ferrero JM et al. Influence of internal mammary node irradiation on long-term outcome and contralateral breast cancer incidence in node-negative breast cancer patients. Radiother Oncol 2013; 108(2): 259–265.
21. Belkacemi Y, Bigorie V, Pan Q et al. Breast radiotherapy (RT) using tangential fields (TgF): a prospective evaluation of the dose distribution in the sentinel lymph node (SLN) area as determined intraoperatively by clip placement. Ann Surg Oncol 2014; 21: 3758–3765.
22. Jagsi R, Chadha M, Moni J et al. Radiation field design in the ACOSOG Z0011 (Alliance) trial. J Clin Oncol 2014; 10(32): 3600–3606.
23. NSABP-B51/RTOG (NCT01872975). Alliance trial (NCT01901094). http://www.clinicaltrials.gov (18 December 2014, date last accessed).
24. Kunkler IH, Audisio R, Belkacemi Y et al. Review of current best practice and priorities for research in radiation oncology for elderly patients with cancer: the International Society of Geriatric Oncology (SIOG) task force. Ann Oncol 2014; 25 (11): 2134–2146.
25. Hughes KS, Schnaper LA, Bellon JR et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. J Clin Oncol 2013; 31(19): 2382–2387.

Annals of Oncology 26: 535–541, 2015
doi:10.1093/annonc/mdu568
Published online 15 December 2014

Role of circulating tumor cells as prognostic marker in resected stage III colorectal cancer

M. J. Sotelo[1,†], J. Sastre[1,†], M. L. Maestro[2,†], S. Veganzones[2,†], J. M. Viéitez[3], V. Alonso[4,†], C. Grávalos[5], P. Escudero[6], R. Vera[7], E. Aranda[8,†], P. García-Alfonso[9,†], J. Gallego-Plazas[10], C. Lopez[11,†], C. Pericay[12], A. Arrivi[13], P. Vicente[14], P. Ballesteros[15], E. Elez[16,†], A. López-Ladrón[17] & E. Díaz-Rubio[1*,†]

Departments of [1]Medical Oncology; [2]Clinical Analysis, Hospital Universitario Clínico San Carlos, Madrid; [3]Department of Medical Oncology, Hospital Universitario Central de Asturias, Oviedo; [4]Department of Medical Oncology, Hospital Universitario Miguel Servet, Zaragoza; [5]Department of Medical Oncology, Hospital Universitario 12 de Octubre, Madrid; [6]Department of Medical Oncology, Hospital Clínico Lozano Blesa, Zaragoza; [7]Department of Medical Oncology, Complejo Hospitalario de Navarra, Pamplona; [8]Department of Medical Oncology, Hospital Reina Sofía, Universidad de Córdoba, Maimonides Institute of Biomedical Research (IMIBIC), Córdoba; [9]Department of Medical Oncology, Hospital Universitario Gregorio Marañón, Madrid; [10]Department of Medical Oncology, Hospital Universitario de Elche, Elche; [11]Department of Medical Oncology, Hospital Universitario Marqués de Valdecilla, Santander; [12]Department of Medical Oncology, Corporació Sanitària Universitària Parc Taulí, Sabadell; [13]Department of Medical Oncology, Hospital Son Llatzer, Palma de Mallorca; [14]Department of Medical Oncology, Hospital de Granollers, Granollers; [15]Department of Medical Oncology, Hospital Universitario Virgen de las Nieves, Granada; [16]Department of Medical Oncology, Hospital Vall dHebrón, Barcelona; [17]Department of Medical Oncology, Hospital Universitario de Valme, Sevilla, Spain

Received 11 September 2014; revised 3 December 2014; accepted 4 December 2014

Background: The prognostic role of circulating tumor cells (CTC) in early colorectal cancer (CRC) has not been determined yet. We evaluated the potential prognostic value of CTC in stage III CRC patients.

Patients and methods: Prospective multicenter study of 519 patients with stage III CRC recruited between January 2009 and June 2010. CTC were enumerated with the CellSearch System after primary tumor resection and before the start of adjuvant therapy. A total of 472 patients were included in the analysis.

Results: CTC ≥1, ≥2, ≥3 and ≥5 were detected in 166 (35%), 93 (20%), 57 (12%) and 34 (7%) patients, respectively. Median follow-up was 40 months. In the overall population, CTC ≥1 (disease-free survival (DFS): HR 0.97, $P = 0.85$; overall survival (OS): HR 1.03, $P = 0.89$), ≥2 (DFS: HR 1.07, $P = 0.76$; OS: HR 1.02, $P = 0.95$), ≥3 (DFS: HR 0.96, $P = 0.87$; OS: HR 0.74, $P = 0.41$) and ≥5 (DFS: HR 0.72, $P = 0.39$; OS: HR 0.48, $P = 0.21$) were not associated with worse DFS and OS. No clinicopathological characteristics were significantly associated with the presence of CTC. In patients with disease relapse, the proportion with CTC ≥1 was not significantly different between those with single versus multiple metastatic locations (37.9% versus 31.4%, $P = 0.761$). In the multivariate analysis, CTC ≥1 was not an independent prognostic factor for DFS (HR 0.97, $P = 0.87$) and OS (HR 0.96, $P = 0.89$).

Correspondence to: Prof. Eduardo Díaz Rubio, Department of Medical Oncology, Fundación de Investigación Biomédica, Hospital Universitario Clínico San Carlos, Universidad Complutense de Madrid, 28040 Madrid, Spain. Tel: +34-91-330-35-46; Fax: +34-91-330-35-46; E-mail: edíazrubio.hcsc@salud.madrid.org

†Centers affiliated to the 'Red Temática de Investigación Cooperativa (RD12/0036/006)(RD12/0036/0012)(RD12/0036/0022)(RD12/0036/0038)(RD12/0036/0076)', Instituto Carlos III, Spanish Ministry of Economy and Competitivity, Madrid, Spain. Spanish Cooperative Group for the treatment of Digestive Tumors (TTD).